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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,374	06/08/2001	Jeffrey C. Rapp	AVI-007	2448

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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,374	RAPP, JEFFREY C.	
	Examiner	Art Unit	
	Thái-An N. Ton	1632	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/25/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-29,62 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-29,62 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 7/25/03, has been entered. Claims 1, 2, 4, 5, 7, 9 and 15 have been amended. Claims 6 and 30-61 have been cancelled. Claims 62 and 63 have been newly added. Claims 1-5, 7-29, 62 and 63 are pending and under current examination.

Specification

The disclosure is objected to because of the following informalities: The term "antibody" is misspelled. See p. 75, line 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-29, 62 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that,

as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The specification fails to describe nucleotide sequences that can produce a polypeptide that can bind selectively to any antigen/immunoglobulin polypeptide, as broadly claimed, with particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art **as of Applicants effective filing date**. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998).

The specification teaches the generation of separate vectors containing cDNA coding for either the heavy or light chain of human monoclonal antibody against CTLA-4 to produce antibodies [see Example 1]. The specification further teaches the transfection of cultured chicken whole embryo fibroblasts with the pCMV-L-

IRES-H plasmid encoding the CTLA-4 human monoclonal antibody [see Example 3]. The specification further teaches the production of the human monoclonal antibody CTLA-4 in chick serum by sperm-mediate transgenesis [Example 4]. Thus, the specification only provides adequate written description for the claimed invention with regard to the human monoclonal CTLA-4 antibody.

In the instant case, the claimed embodiment of a nucleotide sequence that produces an immunoglobulin polypeptide that forms an antibody that selectively binds to an antigen or an immunoglobulin polypeptide lacks a written description. The specification fails to describe what nucleotide sequences fall into this genus when expressed and used as claimed. The skilled artisan cannot envision the detailed chemical structure of all such nucleotide sequences, and therefore conception is *not* achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, because only the human CTLA-4 cDNA was described, it is the only nucleotide sequence meets the written description provision of 35 U.S.C. § 112.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, as written, is unclear. The claim recites that the antibody that is forms selectively binds an antigen or an immunoglobulin peptide, that when combined with its cognate light or heavy chain, forms an antibody that selectively binds an antigen. See lines 7-10. This is unclear because the term "cognate" is defined as similar, or similar in nature. It is unclear how the binding of an antibody combined with a cognate light or heavy chain would result in the production of a heterologous antibody. See preamble. Claims 2-5, 7-29, 62 and 63 depend from claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The prior rejections under 35 U.S.C. §102 have been withdrawn in view of Applicants' amendments and/or arguments. A new rejection appears below.

Claims 1, 2, 4-9, 11, 12, 14-17, 20-29, 62 and 63 are rejected under 35 U.S.C. 102(a) as being anticipated by Ditullio *et al.* [**WO 00/75300 A2**, published June 2, 2000].

Ditullio teach methods of generating transgenic avian. In particular, they teach the introduction of a nucleic acid molecule into the genome of an avian aspecies by contacting *in vivo* a blastodermal cell of a fertilized hard shelled egg [see p. 1-2]. The avian species can be, for example, a chicken [see p. 2, lines 9-12]. DiTullio teach that the nucleic acid can contain a sequence encoding an antibody or fragment thereof, for example, a monoclonal antibody, or a chimeric molecule [*e.g.,* containing antibody portions of both murine and human origin] [see p. 2, lines 22-28]. Ditullio discuss the transcriptional regulatory elements that are contained in the nucleic acid construct, such as initiation signals, enhancers, promoters, which induce or control the transcription of protein coding sequences to which they are operably linked [see p. 3, lines 1-5]. For example, the promoter may be constitutive or inducible, and may be tissue-specific, inducible by external signals or within an intron [see p. 3, lines 12-15]. Ditullio teach that the chicken lysozyme or ovalbumin promoter may be used with the described transgene construct [see p. 3, lines 15-17].

In particular, the invention includes a transgene expression cassette in which the heavy and light chain coding regions of an antibody are ligated together, each under the direction of its own promoter operably linked to a matrix attachment region [see p. 3, lines 24-26]. Ditullio that the avian cell can be targeted either *in vitro* or *in vivo* [see pp. 7-10]. In particular, the cells of the blastoderm can be accessed by cutting or drilling a small hole in the eggshell and directly infusing the DNA into the blastoderm [see p. 7].

Applicants argue that Ditullio does not anticipate because Ditullio does not contain an enabling disclosure. More specifically, Ditullio does not enable a method of producing antibodies. Although aspiring to antibody production in transgenic chicken cells, at most Ditullio demonstrates the introduction of a vector containing the human insulin gene into certain tissues of the chicken by injection of the blastoderm of hard-shell eggs. No expression of insulin protein, much less expression of a multi-chain antibody, is reported. Accordingly, Applicants argue that Ditullio only enables the introduction of nucleic acids comprising a transgene encoding a single polypeptide into a chicken cell. In contrast, claim 1 is directed to a method for the production of an antibody in an avian cell.

Applicants' arguments have been considered, but are not found to be persuasive. MPEP § 2121.01 states that:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention not novel' or anticipated' within section 102, the stated test is whether a reference contains an

> enabling disclosure'... ." In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985).

The methods taught by Ditullio are readily available in the art and would not require undue experimentation. For example, transfection of cells and the transference of these cells to the germinal disc of an unfertilized egg to produce transgenic avian [see p. 7, for example]. There is no requirement for reduction to practice for an invention to be enabling, if one of skill in the art would be able to produce the claimed invention without an undue amount of experimentation. See also MPEP §2164.02.

Accordingly, Ditullio anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 1, 3, 10, 13 under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* [**WO 00/75300 A2**, published June 2, 2000, cited above] when taken with Michael *et al.* [**U.S. Pat. No.** 6,143,559, published November 7, 2000] is *maintained* for reasons of record.

Applicants argue that Ditullio teaches the introduction of insulin coding DNA into cells of a chicken and is not enabling for antibody production. Michael discloses producing chicken monoclonal antibodies, cloning the DNA encoding these chicken antibodies and then expressing the chicken antibodies in cultured mammalian cells, not chicken cells. There is no teaching to express the antibodies in cultured chicken cells. One of ordinary skill in the art would find no clear and particular motivation to combine the two references since Ditullio teaches polypeptide expression in chicken cells while Michael teaches chicken antibody expression in mammalian cells only. Even assuming, arguendo, there were a motivation to combine, Michael does not cure the defects of Ditullio. Ditullio relates to attempting to produce proteins in transgenic chickens while Michael in no way relates to producing any type of transgenic animal. Rather Michael teaches recombinant expression in mammalian cell culture. See p. 11 of Applicants' Response.

Applicants' arguments have been considered, but are not found to be persuasive. The teachings of Ditullio provide sufficient guidance that one of skill in the art would be able to use those teachings with his/her own knowledge to arrive at the claimed invention and there is no requirement for Ditullio to provide the

reduction to practice, because the methods of transfection would have been well known to those skilled in the art.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Michael teaches the generation of monoclonal antibodies in avian species, such as chickens, not chicken antibodies in mammalian cells, as asserted by Applicants. See, for example, col. 2, lines 15-20, 29-40. Particularly by immunizing the chicken with an antigen composition, isolating B cells from the chicken, immortalizing the B cells, selecting an immortalized antibody producing B cell, preparing nucleic acids encoding the antigen binding exons of the light and heavy chains, cloning these binding regions into vectors and then transferring the vectors into a suitable host cell. The antibody sequence can be selected from, for example, human. See col. 3, lines 28-37. Although Michael further teach that the isolated sequences may be expressed in host cells, such as mammalian cells, it would have been obvious for one of skill in the art to express such constructs in an avian cell because the cytomegaloviral promoter is a well-known and well-characterized promoter that

would allow for optimal levels and patterns of gene expression, that utilizing an IRES element would facilitate expression of multiple genes, and that viral transduction is an efficient way to deliver a construct to a cell.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)-872-9306.

TNT

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